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Ethambutol-Induced Visual Disturbance: A Case Report Emphasizing Early Recognition and Management

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Abstract

Ethambutol is a key component of first-line anti-tubercular therapy due to its bacteriostatic activity against Mycobacterium tuberculosis. However, it carries a well-recognized risk of optic neuropathy, which, if not promptly identified, may result in permanent visual impairment. Ethambutol-induced optic neuropathy (EON) is typically dose- and duration-dependent, but cases may also occur at standard dosages in the absence of classical risk factors.

We present the case of a 47-year-old male undergoing standard anti-tubercular treatment who developed progressive bilateral visual disturbances—central scotomas, night blindness, and photophobia—approximately six weeks after initiating therapy. He was receiving ethambutol at a dose of 800 mg/day (approximately 15 mg/kg/day). Clinical suspicion of EON led to immediate discontinuation of ethambutol and substitution with levofloxacin. Causality was assessed as "probable" using both the WHO-UMC system and Naranjo's scale. Although formal ophthalmologic evaluation and follow-up were limited, the temporal relationship, clinical presentation, and dose-response supported the diagnosis.

This case underscores the need for heightened clinical vigilance, routine visual monitoring, and patient education—even in cases adhering to standard treatment guidelines. Given the irreversible nature of delayed-detected EON, baseline and periodic ophthalmologic assessments should be integrated into tuberculosis treatment protocols to facilitate early detection and intervention.

Keywords: Ethambutol, Optic neuropathy, Visual disturbance, Tuberculosis treatment, Adverse drug reaction, Pharmacovigilance.

I. Introduction

Tuberculosis (TB) remains a global health concern, particularly in low- and middle-income countries, where it continues to cause high rates of illness and death. According to the World Health Organization (WHO), over 10 million people were diagnosed with TB in 2022, and the disease remains one of the top causes of infectious mortality worldwide[1].Standard treatment for drug-susceptible TB includes a fixed-dose combination of four first-line drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol.

Ethambutol is an important component of anti-tubercular therapy due to its bacteriostatic effect against *Mycobacterium tuberculosis*. It works by inhibiting arabinosyl transferase, an enzyme involved in the synthesis of the mycobacterial cell wall [2].However, despite its effectiveness, ethambutol is associated with a known adverse effect: **optic neuropathy**, which may lead to vision disturbances.

Ethambutol-induced optic neuropathy (EON) is dose- and duration-dependent and may present with symptoms such as decreased visual acuity, colour vision defects, central scotomas, and night blindness [3], [4].Although the condition can be reversible if identified early and the drug is discontinued promptly, delayed diagnosis may result in permanent visual impairment [5].

Risk factors for EON include high doses of ethambutol (typically >15 mg/kg/day), prolonged use beyond two months, pre-existing kidney disease, advanced age, and low body weight [6], [7]. **The underlying mechanism** is thought to involve disruption of mitochondrial function in retinal ganglion cells, caused by the drug's metal-chelating properties [8].

Due to the potential severity of this side effect, regular visual monitoring is recommended during ethambutol therapy, especially in high-risk patients. Early detection through simple clinical tools such as visual acuity testing and colour vision screening can help prevent long-term complications [9].

II. Case Summary

A 47-year-old male patient, weighing 53 kg, with a recent diagnosis of pulmonary tuberculosis, was initiated on standard first-line anti-tubercular therapy under a directly observed treatment strategy. His regimen included ethambutol 800 mg once daily, along with a fixed-dose combination of isoniazid 300 mg and rifampicin 450 mg once daily, and

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pyrazinamide 500 mg once daily. He had no history of chronic illnesses such as diabetes, hypertension, or renal disease, and baseline ophthalmologic assessment was not performed prior to treatment initiation.

Approximately six weeks into therapy, the patient began experiencing gradual onset of visual symptoms. He reported the presence of dark spots (scotomas) in his central visual field, difficulty seeing at night (nyctalopia), and photophobia. These symptoms were associated with intermittent dizziness and headaches, which were aggravated by exposure to bright light. The patient described no pain with eye movements, and there was no redness, tearing, or discharge. There was no history of similar symptoms in the past or of ocular trauma.

Given the timeline and clinical presentation, ethambutol-induced optic neuropathy (EON) was suspected. While formal ophthalmologic testing including visual fields, fundus examination, and optical coherence tomography (OCT) was not available at the time of evaluation, the constellation of symptoms—particularly the bilateral nature, central visual defects, and photosensitivity—supported the diagnosis. The patient had been receiving ethambutol at a dose of approximately 15 mg/kg/day, which is at the upper limit of recommended dosing. Although his renal function appeared normal, no serum creatinine or creatinine clearance documentation was available to assess for drug accumulation risk.

Ethambutol was promptly discontinued from the treatment regimen, and the patient was started on levofloxacin 750 mg once daily to maintain adequate anti-tubercular coverage. No specific therapy was initiated for optic neuropathy, such as corticosteroids or neuroprotective agents, as there is no proven treatment for EON beyond drug withdrawal.

Causality assessment was performed using multiple standardized tools. The **WHO-Uppsala Monitoring Centre (WHO-UMC) scale** and the **Naranjo Adverse Drug Reaction Probability Scale** with a score of **7**, both categorized the event as "probable." The **Karch and Lasagna criteria** also supported a temporal and pharmacological link between ethambutol use and the adverse event. The reaction was assessed as **moderate (Level 4b)** using severity grading criteria, since it necessitated discontinuation of the suspected drug and modification of the therapeutic regimen.

Figure 1: Naranjo's scale (This image should appear after 5th paragraph)

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given? *	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total Score:	7

*Question 6 refers to a typical clinical trials situation and is included here for completeness.

Total Score	Interpretation of Scores
≥ 9	Definite. The reaction (1) followed a reasonable temporal sequence after drug exposure had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, (3) was confirmed by improvement on withdrawing the drug and (4) reappeared on reexposure.
5 - 8	Probable. The reaction (1) followed a reasonable temporal sequence after a drug exposure, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
1 - 4	Possible. The reaction (1) followed a temporal sequence after a drug exposure, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
≤ 0	Doubtful. The reaction was likely related to factors other than a drug.

The Naranjo scale is a tool to help clarify how to evaluate a potential causal association. It is not intended to solve all the complex problems of identification and classification of ADRs.

Adapted from: https://www.robsonforensic.com/articles/adverse-drug-reactions-expert-article

The adverse event was considered **predictable and likely preventable**, especially with appropriate risk stratification and routine visual function monitoring, which had not been conducted at treatment initiation or during follow-up. The patient was advised to attend regular ophthalmology follow-up visits to monitor visual recovery. However, due to limited follow-up data, the eventual outcome—whether full, partial, or no recovery of visual function—remains unknown.

This case highlights the importance of incorporating baseline and periodic visual assessment in patients receiving ethambutol, particularly in those with risk factors such as high-dose therapy, prolonged treatment duration, older age, or renal impairment. Early recognition and withdrawal of the offending agent remain the cornerstone of preventing permanent visual damage.

III. DISCUSSION

Ethambutol-induced optic neuropathy (EON) is a recognized but often underreported adverse drug reaction. Although the risk is considered low at standard therapeutic doses (15 mg/kg/day), the condition can be serious and lead to irreversible visual loss if not identified and managed early [4]. In most cases, the onset of visual symptoms occurs within 4 to 12 weeks of starting therapy, but earlier or later presentations have also been observed

depending on individual susceptibility and cumulative drug exposure [6], [9].
The **pathophysiology** of EON is not fully understood, but it is thought to involve mitochondrial dysfunction in retinal ganglion cells. Ethambutol is a metal chelator that may interfere with copper- and zinc-dependent enzymes essential for energy metabolism in the optic nerve [8].This disruption impairs mitochondrial oxidative phosphorylation, leading to axonal degeneration and subsequent vision changes. Histologically, damage to the papillomacular bundle is often noted, which corresponds clinically to central vision loss and dyschromatopsia [3], [8].
Symptoms typically include blurred vision, reduced visual acuity, central or cecocentral scotomas, difficulty distinguishing colours (particularly red-green), and photophobia. Night blindness or nyctalopia, although less common, may also occur as part of early optic nerve dysfunction [3], [6]. The visual deficits are usually bilateral and symmetrical, although one eye may be affected more than the other at the onset.
Several risk factors have been associated with increased likelihood of EON. These include:

- High ethambutol doses (>15–20 mg/kg/day),
- Prolonged treatment duration (>2 months),
- Pre-existing renal insufficiency (leading to drug accumulation),
- Advanced age,
- Low body weight,
- Co-administration of other neurotoxic drugs [5] [7].

Prompt discontinuation of ethambutol is the most important step once EON is suspected. In many cases, this leads to gradual improvement of symptoms over a period of weeks to months, although some visual deficits may persist even after stopping the drug [10], [11]. The extent of recovery depends on how early the condition is recognized and whether there is any pre-existing optic nerve damage. Studies have reported partial or full recovery in 60–80% of cases when the drug is withdrawn early [10].

There is no specific antidote or curative therapy for EON. Supportive treatments, such as vitamin B-complex or antioxidants, have been used in some cases, but their effectiveness remains uncertain [12].Therefore, prevention through early detection and dose adjustment remains the most effective strategy.

Routine ophthalmologic monitoring is strongly recommended, especially for high-risk patients. Baseline visual acuity and colour vision testing should be performed before starting ethambutol. Monthly follow-up using simple tools like the Ishihara colour test, Snellen chart, and Amsler grid can help detect early signs of optic nerve dysfunction. Where available, advanced diagnostics such as **optical coherence tomography (OCT)** and **visual evoked potentials (VEPs)** can detect structural and functional changes in the optic nerve even before symptoms become evident [13], [14].

In clinical settings with limited resources, even basic visual assessments can be valuable. Educating patients to report symptoms like blurry vision, trouble reading, difficulty seeing at night, or changes in colour perception is equally important. Early recognition can help prevent long-term complications and improve patient outcomes.

With the increased use of fixed-dose combination (FDC) anti-tubercular regimens that include ethambutol for the full 6-month treatment course, the risk of delayed recognition of EON may be higher. Therefore, clinicians must maintain a high level of suspicion and consider stopping ethambutol at the earliest sign of visual toxicity. Pharmacovigilance systems should also be strengthened to capture and report such adverse events.

IV. CONCLUSION

Ethambutol-induced optic neuropathy is a serious yet preventable complication of tuberculosis therapy. In this case, visual symptoms developed within weeks of starting standard-dose treatment, emphasizing that toxicity can occur even without classical risk factors. Prompt recognition and discontinuation of the drug are critical to minimizing long-term visual damage.

This case underscores the importance of integrating baseline and regular visual monitoring into TB treatment protocols, particularly in high-risk patients. Simple tools like Snellen charts and colour vision tests can aid early detection. Clinician vigilance and patient education on early visual symptoms are essential components of safe ethambutol use and can significantly reduce the risk of irreversible vision loss.

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